REMARKS

Applicants have amended claims 54 and 62 and added new claims 70 to 80. No new matter is presented.

Information Disclosure Statement

The PTO-1149 form of 10-28-02 was incorrectly marked "Sheet Page 1 of 2." The form is a single sheet. A new PTO-1449 form to replace the form of 02-14-03 is attached containing the requested information for reference 100 i.e. the February 27, 1996 publication date.

35 USC 103(c) Rejection

The Examiner rejected claims 1, 2 and 35-69 under 35 USC 103(c) as unpatentable over Hepar Industries Inc in view of Nielsen. The heparin fractions described in Hepar differ significantly from the MMWH compositions of the present invention. Hepar discloses a method of preparing heparin fractions by oxidative cleavage of heparinic acid using an oxidizing agent such as a peroxide at elevated temperatures in an autoclave. Heparin fractions are selected based on anti-Xa/APTT activity.

In contrast, the claimed MMWH composition of the invention is characterized by a greater uniformity of oligosaccharides with different properties than the diverse heparin fractions prepared by Hepar. In particular, the MMWH compositions of the present invention are not selected based on anti-Xa/APTT activity, and they are enriched for pentasaccharide sequence that interacts or binds with antithrombin, which is not trivial to obtain as asserted by the Examiner. Even if one were to modify the Hepar disclosure to adjust for molecular weight as

alleged, the resultant modified Hepar mixture would still lack the enriched pentasaccharide feature recited in the claims.

A skilled artisan could not produce a composition with the enriched pentasaccharide or other properties (e.g. anti-IIa activity, molecular weight range) of the claimed MMWH composition using the procedure described in Hepar. Notably the procedure described in Hepar reduces the pentasaccharide content of the resultant heparin fragments because it utilizes oxidative agents and high temperature for depolymerization. The harsh depolymerization method of Hepar provides desulfated heparin fragments. Because the pentasaccharide sequence is the most heavily sulphated portion of the heparin molecule it is particularly prone to desulfation. In fact, the final step in the Hepar process involves resulfation in an attempt to restore the sulphate groups that are essential for heparin's interaction with antithrombin. However, resulfation is an uncontrolled and random process that (a) will be variable from batch to batch, and (b) may or may not resulfate the saccharide residues within the pentasaccharide sequence. Critical for heparin's interaction with antithrombin is the 3-0-sulfated glucosamine residue in the middle of the pentasaccharide sequence (Atha DA et al., Biochemistry 24:6723, 1985; Choay et al., Biochem. Biophys. Res. Commun. 116:492,1983; Lindahl U. et al., J. Biol. Chem. 259;12368, 1984). This residue is particularly difficult to resulfate because the amino group at the C-2 position (which also is sulfated) will sterically hinder 0-sulfation at the adjacent C-3 position. Thus, the heparin fragments described in Hepar have reduced anticoagulant activity.

The particular MMWH compositions of present claims 70-74 may also be further distinguished from Hepar as they are prepared by enzymatic cleavage using heparinase which provides a more specific cleavage resulting in a highly uniform composition.

The deficiencies of Hepar are not addressed in Nielsen. Nielsen relates to a method of monitoring a heparinase depolymerization process using UV-absorption and refractive index to obtain low molecular weight heparin of a predetermined average low molecular weight (6500±500) with reduced polydispersity. The monitoring method is of little practical utility, and would not provide compositions with the molecular weight ranges and polydispersity of the claimed MMWH compositions. In particular, The MMWH compositions of the present claims, (in particular, claims 38, 39, 40, 50, 51, 52, 54, 56, and claims depending therefrom, and claims 70 to 80) can be distinguished based on properties including molecular weight (e.g. 8000 to 10000 MW range) and polydispersity (e.g, 1.1 to 1.5).

It is respectfully submitted to be apparent that the Examiner's prior art rejections are untenable. Withdrawal of the rejections and allowance of this application are respectfully requested.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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